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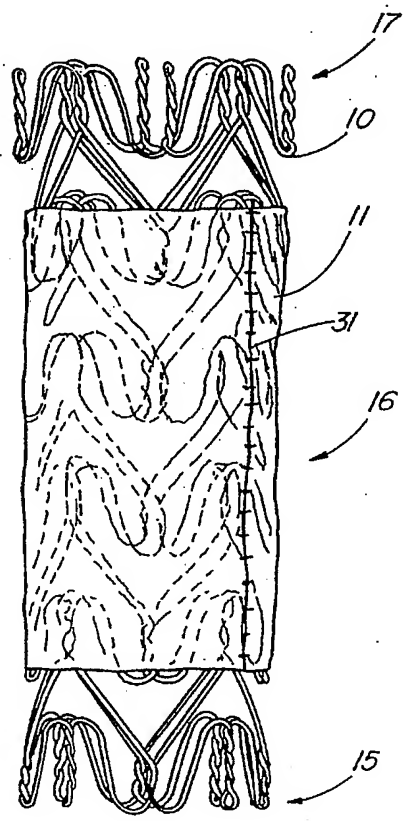
(57) Abstract

A graft construct and method for repairing the inner linings of damaged or diseased vessels is described. The method comprises the steps of positioning a graft construct within a blood vessel at a site in need of repair. The graft construct comprises purified submucosa removed from a submucosa tissue source.



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STENT GRAFTS CONTAINING PURIFIED SUBMUCOSA

Description

Technical Field

This invention relates to a purified tela submucosa covered prosthesis useful in promoting the resurfacing and repair of damaged or diseased tissue structures. More particularly, this invention is directed to stents having a layer of purified submucosa covering a surface of the stent, and their use in repairing damaged or diseased physiological vessels, particularly blood vessels.

Background of the Invention

The most common cause of vascular disease in the Western world is atherosclerosis, in which cholesterol and fibrous tissue, often together with calcium precipitates, gradually build up within the inner layers of the arterial wall, diminishing the cross-sectional area available for blood flow. There are two essential abnormalities of such atherosclerotic lesions that cause complications. The first is the narrowing of the lumen, which produces a chronic limitation of blood flow distally. The second is the abnormally raised, roughened inner surface of the artery, the physical properties of which tend to induce platelet adhesion and clot formation at the diseased site. Thrombosis can produce sudden cessation of blood flow with disastrous consequences for downstream organs such as the brain, heart muscle, kidney, or lower extremities. The eroded, abnormal intimal surface of sclerotic vessels causes additional complications including fragmentation of atherosclerotic material with downstream embolization and hemorrhage or dissection of blood into the plaque itself causing sudden expansion of the lesion and occlusion of the vessel.

Another consequence of vascular disease is aneurysmal formation in the vessel wall. As disease weakens the vessel wall an aneurysmal sac evolves leading to eventual rupture of the vessel wall and death of the patient. By blocking the neck or opening to the aneurysm, flowing blood is excluded from the aneurysm, the vessel wall is reinforced and vessel rupture is avoided. Another treatment for aneurysmal vessels is to purposefully occlude the aneurysmal segment and bypass the

aneurysmal segment with a graft. A prosthesis as described herein can serve this purpose.

Percutaneous transluminal angioplasty (PTA), first performed 25 years ago by Dotter and Judkins, is the technique of opening narrowed or occluded blood vessels by passing guide wires and catheters through the stenotic or occluded portion of the blood vessel. Dotter's original PTA method involved inserting increasingly larger catheters over a guidewire to progressively dilate the vessel. Later modifications utilized graduated catheters with gradually tapering tips, which created more lateral compression and less longitudinal shearing action. These early PTA procedures were limited by the requisite stiffness of the catheters and by the large puncture wounds required for the procedure.

In 1974, PTA procedures were revolutionized by the introduction of balloon catheter angioplasty. A balloon catheter has an expandable sac that can be expanded and contracted in a controlled manner in response to inflation pressure. Balloon catheter angioplasty involves positioning the balloon catheter at a stenotic site and inflating the sac to a predetermined size to open the stenotic or occluded portion of the blood vessel. The sac is then deflated and the catheter removed leaving a larger lumen. However standard balloon angioplasty, with or without the use of stents, produces a torn vessel with myointimal flaps and exposed fissures. These provide thrombogenic surfaces and sites for hemodynamic dissection. Alternative techniques for removing atherosclerotic plaques include laser angioplasty and mechanical arthrectomy devices, which can vaporize, melt, or remove plaque material. However, all such systems leave an abnormal, thrombogenic surface.

Angioplasty is now known to damage the vessel wall by tearing and stretching, this form of controlled injury opens the vessel lumen and increases blood flow acutely in nearly all cases. However, abrupt vessel closure, during or immediately following PTA, and late restenosis continue to limit the effectiveness of the procedure. To enhance the efficacy of PTA procedures, catheters have been fitted with vascular stents.

Stents are three dimensional implantable structures that (upon delivery to an intra-vessel position) physically hold a blood vessel open. Vascular stents are

typically formed to fit on the end of conventional catheters for delivery of the stent to a predetermined intravascular location. Preferably, stents used in conjunction with PTA are "expandable stents" having an initial collapsed state that allows the stent to be delivered to the desired intravascular location with minimal longitudinal shearing action. Upon delivery to the desired location, the stent is expanded to fix the stent at that location and to physically hold the vessel open.

A number of stents for coronary use are commercially available. They differ in physicochemical characteristics and the mode of implantation. Ideally, a stent should be flexible, thrombo-resistant, low in profile, radiopaque, limit the expansion of repair tissues into the lumen of the vessel, and have an easy, reliable delivery system. Table 1 provides a list of several stents suitable for use in accordance with the present invention; however, the list is not exhaustive and additional stents known to those skilled in the art can be used in accordance with the present invention.

Table 1. Design and Characteristics of Stents in Clinical Evaluation

Stent	Configuration	Filament Composition	Filament Thickness (mm)	Stent Diameter (mm)	Stent Length (mm)	Surface Area (%)	Radiopaque
Self-expanding							
Wallset	Wire-mesh	Stainless Steel	0.07-0.10	3.5-6.0	21-45	18.5-20	No
Balloon-expandable							
Palmaz-Schatz	Slotted tube	Stainless Steel	0.08	3.0-4.0	15	10	No
Gianturco-Roubin	Incomplete coil	Stainless Steel	0.15	2.0-4.0	20	10	No
Wiktok	Helical coil	Tantalum	0.125	3.0-4.0	15-17	5-10	Yes
Streker	Woven wire	Stainless steel/tantalum	0.07	2.0-3.5	15-25	--	No Yes

Currently available expandable stents can be categorized as "self expandable stents" and "balloon expandable stents." Self expanding stents utilize a spring mechanism to constrain the stent to a compressed shape. Upon removal of the constraint, the stent expands to a predetermined dimension. Balloon expandable stents are expandable members formed to fit over a balloon catheter and capable of being expanded in response to controlled inflation of the balloon catheter. Inflation of the balloon results in plastic deformation of the stent beyond its elastic limits so that the stent remains in its expanded state upon subsequent deflation and removal of the balloon catheter.

Although the presently available stents can be implanted to give highly predictable immediate angiographic results, those stents all suffer the disadvantage that they have limited long-term efficacy. Despite holding the vessel open, the natural reparative processes at a stent-dilated vessel result in healing tissues growing around the stent structure and eventually occluding the lumen of the vessel.

The present invention utilizes a natural collagenous matrix comprising purified submucosa in combination with known angioplastic techniques to eliminate complications that derive from the residual abnormal, thrombogenic surfaces produced by current available angioplastic techniques such as ordinary balloon angioplasty, laser angioplasty, and transluminal mechanical arthrectomy. The collagenous matrices for use in accordance with the present invention comprise highly conserved collagens, glycoproteins, proteoglycans, and glycosaminoglycans in their natural configuration and natural concentration.

In accordance with the present invention, the purified submucosa is isolated from warm-blooded vertebrate tissue including the alimentary, respiratory, urinary or genital tracts of warm-blooded vertebrates. The preparation of intestinal submucosa is described and claimed in U.S. Patent No. 4,902,508, and the preparation of purified tela submucosa is described and claimed in U.S. Patent Application No. 08/916,490, filed August 22, 1997, the disclosure of which is expressly incorporated herein by reference. Preferred purified submucosas for use in accordance with this invention include purified intestinal submucosa, purified

stomach submucosa, purified urinary bladder submucosa, and purified uterine submucosa.

As a tissue graft, purified submucosa undergoes remodeling and induces the growth of endogenous tissues upon implantation into a host. It has been used successfully in vascular grafts, urinary bladder and hernia repair, replacement and repair of tendons and ligaments, and dermal grafts. The preparation and use of submucosa as a tissue graft composition is described in U.S. Patent Nos. 4,902,508; 5,281,422; 5,275,826; 5,554,389, and other related U.S. patents. The preparation and use of purified submucosa as a collagen-based, matrix structure graft composition is described in U.S. Patent Application No. 08/916,490. When used in such applications, the graft constructs appear not only to serve as a matrix for the regrowth of the tissues replaced by the graft constructs, but also promote or induce such regrowth of endogenous tissue. Common events to this remodeling process include: widespread and very rapid neovascularization, proliferation of granulation mesenchymal cells, biodegradation/resorption of implanted intestinal purified submucosa material, and lack of immune rejection. The use of purified submucosa in sheet form and fluidized forms for inducing the formation of endogenous tissues is described and claimed in U.S. Patent Application No. 08/916,490, the disclosures of which are expressly incorporated herein by reference.

Summary of the Invention

The present invention is directed to an improved prosthetic device for repairing the wall or surface of damaged or diseased vessels. The prosthetic devices of the present invention can also be used in traditional PTA procedures to open narrowed or occluded vessels. In one embodiment, the prosthetic device comprises an elongated shaped expandable member having a luminal and exterior surface, and a layer of collagen-based matrix structure removed from a submucosa source fixed to at least one of the exterior and luminal surfaces of the member. The expandable member is typically a stent wherein expansion of the stent increases the circumference of said member, thus fixing the device at a predetermined location within the vessel.

Brief Description of the Drawings

FIG. 1 is a cross-sectional view of a balloon catheter carrying a purified submucosa coated stent in accordance with this invention.

FIG. 2 illustrates another purified submucosa-carrying stent of this invention.

FIG. 3 illustrates a stent-carrying purified submucosa slit to allow blood flow in branched vessels in both open and closed configurations.

FIGs. 4 and 5 illustrate strips of purified submucosa or fluidized, purified submucosa covering a wire prior to making a stent from the wire.

FIG. 6 and 7 depict another stent construct of this invention, wherein the stent is made from wire coated with purified submucosa.

FIG. 8 illustrates a patch of purified submucosa mounted to a stent.

FIG. 9 illustrates a stent covered on its exterior surface with purified submucosa and a section of said submucosa has been removed to allow fluid communication between the inside and outside of the stent.

FIG. 10 illustrates a stent covered with purified submucosa where said submucosa extends beyond the end of the stent and is suspended taut across the lumen of the stent.

FIG. 11 illustrates a band of purified submucosa in the form of a tube overlying a stent.

FIG. 12 illustrates an end view of a pleated sheet of purified submucosa overlying a stent.

Detailed Description

The present invention is directed to an improved vascular stent composition and a method for repairing the inner linings of damaged or diseased vessels. The method comprises the step of applying a new, non-thrombogenic intimal surface of purified submucosa over the former damaged or diseased intima. The term "vessel" as used herein is defined as including any bodily canal, conduit, duct or passageway, including but not limited to blood vessels, bile ducts, the esophagus, the trachea, the ureter and the urethra. In one embodiment, the vessel is expanded to increase the lumen of the vessel simultaneously with the application

of a layer of purified submucosa. Applicants have discovered that the applied purified submucosa layer provides a non-thrombogenic surface that induces the formation of a new endothelium and inhibits restenosis of a vessel after expansion of the vessel.

For the purpose of promoting an understanding of the principles of the invention, reference will now be made to certain preferred embodiments thereof and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations, further modifications and applications of the principles of the invention as described herein being contemplated as would normally occur to one skilled in the art to which the invention relates.

In the discussions herein, a number of terms are used. In order to provide and clear and consistent understanding of the specification and claims, the following definitions are provided.

Bioburden - refers to the number of living microorganisms, reported in colony-forming units (CFU), found on and/or in a given amount of material. Illustrative microorganisms include bacteria, fungi and their spores.

Disinfection - refers to a reduction in the bioburden of a material.

Sterile - refers to a condition wherein a material has a bioburden such that the probability of having one living microorganism (CFU) on and/or in a given section of the material is one in one-million or less.

Pyrogen - refers to a substance which produces febrile response after introduction into a host.

Endotoxin - refers to a particular pyrogen which is part of the cell wall of gram-negative bacteria. Endotoxins are continually shed from the bacteria and contaminate materials.

Purification - refers to the treatment of a material to remove one or more contaminants which occur with the material, for instance contaminants with which the material occurs in nature, and/or microorganisms or components thereof occurring on the material. Illustratively, the contaminants may be those known to

cause toxicity, infectivity, pyrogenicity, irritation potential, reactivity, hemolytic activity, carcinogenicity and/or immunogenicity.

Biocompatibility - refers to the ability of a material to pass the biocompatibility tests set forth in International Standards Organization (ISO) Standard No. 10993 and/or the U.S. Pharmacopeia (USP) 23 and/or the U.S. Food and Drug Administration (FDA) blue book memorandum No. G95-1, entitled "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing." Typically, these tests assay as to a material's toxicity, infectivity, pyrogenicity, irritation potential, reactivity, hemolytic activity, carcinogenicity and/or immunogenicity. A biocompatible structure or material when introduced into a majority of patients will not cause an adverse reaction or response. In addition, it is contemplated that biocompatibility can be effected by other contaminants such as prions, surfactants, oligonucleotides, and other biocompatibility effecting agents or contaminants.

Contaminant - refers to an unwanted substance on, attached to, or within a material. This includes, but is not limited to: bioburden, endotoxins, processing agents such as antimicrobial agents, blood, blood components, viruses, DNA, RNA, spores, fragments of unwanted tissue layers, cellular debris, and mucosa.

Tela submucosa - refers to a layer of collagen-containing connective tissue occurring under the mucosa in most parts of the alimentary, respiratory, urinary and genital tracts of animals.

As disclosed above, the present invention generally provides graft prostheses and materials including a purified collagen-based matrix structure, and methods for obtaining and using the same. Advantageous graft prostheses of the invention are obtained from a submucosa tissue source, for example including animal tissues such as human or other mammalian tissues, e.g. porcine, bovine or ovine tissues.

Tela submucosa, as with many animal tissues, is generally aseptic in its natural state, provided the human or animal does not have an infection or disease. This is particularly the case since the tela submucosa is an internal layer within the alimentary, respiratory, urinary and genital tracts of animals. Accordingly, it is

generally not exposed to bacteria and other cellular debris such as the epithelium of the intestinal tract. One feature of the present invention is the discovery that by disinfecting the source tissue for the tela submucosa prior to delamination, the aseptic state of the tela submucosa layer can be preserved or substantially preserved, particularly if the delamination process occurs under sterile conditions.

In particular, it has been discovered that disinfecting the tela submucosa source, followed by removal of a purified matrix including the tela submucosa, e.g. by delaminating the tela submucosa from the tunica muscularis and the tunica mucosa, minimizes the exposure of the tela submucosa to bacteria and other contaminants. In turn, this enables minimizing exposure of the isolated tela submucosa matrix to disinfectants or sterilants if desired, thus substantially preserving the inherent biochemistry of the tela submucosa and many of the tela submucosa's beneficial effects.

A tela submucosa implantable collagen matrix according to the present invention can, as indicated above, be obtained from the alimentary, respiratory, urinary or genital tracts of animals. Preferably, the tela submucosa tissues, which are collagen-based and thus predominantly collagen, are derived from the alimentary tract of mammals and most preferably from the intestinal tract of pigs. A most preferred source of whole small intestine is harvested from mature adult pigs weighing greater than about 450 pounds. Intestines harvested from healthy, nondiseased animals will contain blood vessels and blood supply within the intestinal tract, as well as various microbes such as *E. coli* contained within the lumen of the intestines. Therefore, disinfecting the whole intestine prior to delamination of the tela submucosa substantially removes these contaminants and provides a preferred implantable tela submucosa which is substantially free of blood and blood components as well as any other microbial organisms, pyrogens or other pathogens that may be present. In effect, this procedure is believed to substantially preserve the inherent aseptic state of the tela submucosa, although it should be understood that it is not intended that the present invention be limited by any theory.

It is also desirable that the collagen matrix according to the present invention be substantially free of any antibiotics, antiviral agents or any antimicrobial

type agents which may affect the inherent biochemistry of the matrix and its efficacy upon implantation. In the past, one method of treating such material is to rinse the delaminated matrix in saline and soak it in an antimicrobial agent, for example, as disclosed in U.S. Patent No. 4,956,178. While such techniques can optionally be practiced with isolated submucosa of the present invention, preferred processes according to present invention avoid the use of antimicrobial agents and the like which may not only affect the biochemistry of the collagen matrix but also can be unnecessarily introduced into the tissues of the patient.

As discussed above, it has been discovered that a highly pure form of an implantable tela submucosa collagen matrix may be obtained by first disinfecting a tela submucosa source prior to removing a purified collagen matrix including the tela submucosa layer, e.g. by delaminating the tela submucosa source. It has also been discovered that certain processing advantages as well as improved properties of the resultant tela submucosa layer are obtained by this process, including greater ease in removing attached tissues from the submucosa layer, and a characteristic, low contaminant profile.

The preparation of submucosa is described in U.S. Patent No. 4,902,508, and, more particularly, the preparation of purified submucosa for use in accordance with the present invention is described in U.S. Patent Application No. 08/916,490 filed August 22, 1997, titled "Graft Prosthesis, Materials and Methods" which claims priority to and incorporates herein by reference Serial No. 60/024,693, filed September 9, 1996, titled "A Highly Purified Tela Submucosa Implantable Tissue," and Serial No. 60/024,542, filed August 23, 1996, titled "A Substantially Purified Tela Submucosa Implantable Tissue."

The purified submucosa of the present invention can be sterilized using conventional sterilization techniques including glutaraldehyde tanning, formaldehyde tanning at acidic pH, propylene oxide treatment, gas plasma sterilization, gamma radiation, electron beam radiation, ethylene oxide, and peracetic acid sterilization. Sterilization techniques which do not adversely affect the mechanical strength, structure, and biotropic properties of the purified submucosa is preferred. For instance, strong gamma radiation may cause loss of strength of the sheets of purified

submucosa. Preferred sterilization techniques include exposing the graft to peracetic acid, 1-4 Mrads gamma irradiation (more preferably 1-2.5 Mrads of gamma irradiation) or gas plasma sterilization; peracetic acid sterilization is the most preferred sterilization method.

The purified submucosa specified for use in accordance with this invention can also be in a fluidized form. The preparation of fluidized forms of purified submucosa is described in U.S. Patent Application No. 08/916,490, the disclosure of which is expressly incorporated herein by reference.

Purified submucosa can be stored in a hydrated or dehydrated state. Lyophilized or air dried purified submucosa can be rehydrated and used in accordance with this invention without significant loss of its biotropic and mechanical properties.

Purified submucosa can be used in accordance with the present invention in combination with standard PTA devices to form prosthetic devices suitable for use in PTA procedures. Applicants anticipate that the use of the present graft constructs comprising purified submucosa will enhance the repair of damaged or diseased vessels and thus improve the effectiveness of PTA procedures. The method of repairing vessels *in vivo* through the use of the disclosed devices comprises the steps of contacting the intimal surface of the vessel with purified submucosa and holding the purified submucosa in place to provide a new intimal surface. Advantageously, the implanted layer of purified submucosa induces the growth of new endothelium without stenosis, and therefore the purified submucosa is preferably held in contact with the site in need of repair for a time sufficient to induce the formation of a new intimal surface. In preferred embodiments the graft construct is permanently located within a blood vessel or other structure and is ultimately replaced by endogenous cell growth.

In one embodiment of the present invention, purified submucosa is used in combination with known angioplastic techniques and devices to provide an improved composition and method for repairing damaged or diseased portions of vessels. The improvement method comprises fixing a graft construct comprising purified submucosa onto the surface of a catheter and delivering the graft construct to a predetermined intra-vessel location. It is anticipated that the vessel walls of any

bodily vessel, conduit, canal, or body cavity that is accessible to a catheter, can be repaired using the method described in the present invention.

Conventional catheters can be used to position the purified submucosal graft constructs to an intravessel location for contact with a diseased or damaged surface of the vessel. In accordance with one embodiment, the catheter is a balloon catheter, and the balloon portion is covered with purified submucosa. Upon positioning of the purified submucosa covered catheter within a vessel, inflation of the balloon presses the purified submucosa against the intima surface of the vessel. Subsequent deflation of the balloon portion allows the removal of the catheter, leaving the purified submucosa positioned in contact with the intima surface of the vessel.

The purified submucosa is preferably combined with additional elements to enhance the retention of the purified submucosa layer on the original intimal surface including, use of anchoring projections (such as plastic or metal pins), adhesives, stents, or other fixation devices known to those skilled in the art. In preferred embodiments, the purified submucosa is held in contact with the intimal surface through the use of a mechanical stent.

In accordance with one embodiment an improved stent is provided for opening occluded vessels. The improved stent comprises a conventional expandable stent, wherein the exterior surface of the stent is covered with purified submucosa. Upon deployment of the purified submucosa covered stent, the purified submucosa covers the original intimal surface of the vessel to provide a smooth, non-thrombogenic surface. For example, in one embodiment (FIG.1) the exterior surface of a stent 10 is covered with purified submucosa 11 and a catheter 12 is used to position the stent to a predetermined location in a blood vessel. The stent is expanded, and thereby expands the lumen of the vessel, and the purified submucosa is pressed against the luminal surface of the vessel thus covering the arteriosclerotic lesions and the surface of blood vessels damaged through the angioplasty procedure.

In one embodiment (FIG.8), an improved stent 13 comprises a conventional expandable stent 10, wherein only a portion of the exterior of the stent is covered with purified submucosa 11. Upon deployment of the purified submucosa

covered stent, the purified submucosa covers an area of the original intimal surface of the vessel to provide a smooth, non-thrombogenic surface and separate flowing blood from the original internal surface of the vessel. For example, in one embodiment a portion of the exterior surface of the stent is covered with purified submucosa band delivered over an aneurysm such that the portion of the stent covered with purified submucosa is placed to separate the flowing blood and the aneurysm, thereby treating the aneurysm. For example, in another embodiment (FIG.11), an improved stent 14 comprises a conventional expandable stent 10 having a proximal end portion 15, a central section 16 and a distal end section 17 wherein the central portion of the external surface of the stent is covered with purified submucosa 11 allowing the non-central end portion of the external surface of the stent to be without purified submucosa to promote the attachment of improved stent to the vessel surface.

Returning to FIG. 1, a prosthetic device is depicted that utilizes a stent that incorporates a conventional balloon angioplasty catheter around which are placed, in order, an expandable vascular stent, and a layer of purified submucosa. Alternatively (FIG.2), the stent 10 can be sandwiched between two layers of purified submucosa 18, 19 (i.e., one layer 18 covering the luminal surface 21 of the stent and one layer 19 covering the external surface 22 of the stent). The purified submucosa is immobilized onto the stent through the use of adhesives, sutures 20, interweaving the matrix structure with the stent struts, or other fixation techniques known to those skilled in the art.

The graft constructs of the present invention can be utilized in combination with conventional prosthetic devices known to those skilled in the art as being useful for vessel repair. For example, the purified submucosa constructs of the present invention are fixed onto the distal end of a prosthetic device, such as a catheter, using a variety of techniques including: frictional engagement, applying the purified submucosa onto the surface of the prosthetic device followed by drying the material, suturing the matrix structure to the device, and other means known to those skilled in the art.

In one preferred embodiment, the graft construct comprises an expandable cylindrical shaped member that has purified submucosa covering at least the external surface of the member. In this embodiment, the lumen of the cylindrical member is sized for receiving the distal end of a catheter, and more preferably, the expandable member is formed to frictionally engage the exterior surface of the distal end of the catheter. The expansion of the expandable member increases the circumference of the cylindrical shaped member thus fixing the purified submucosa against the luminal surface of the vessel and allowing for the removal of the catheter after deployment of the graft construct.

In one embodiment, the catheter comprises a balloon-type catheter and the expandable member comprises a stent that is expanded to a fixed enlarged size by the inflation of the balloon catheter. In this embodiment, inflation of the purified submucosa/stent-covered balloon catheter accomplishes several therapeutic objectives, almost simultaneously. First, as in conventional balloon angioplasty, the lumen is forcibly dilated to reverse narrowing caused by an atherosclerotic plaque. Second, the vascular stent maintains the expanded caliber of the vessel, providing a degree of rigid support and maintaining a circular, isodiametric cross-sectional profile. In addition the stent, in combination with intra-arterial pressure, holds the purified submucosa against the intima surface of the vessel covering any cracks, fissures, or tears in the vessel that result during balloon inflation. Such defects in blood vessels are highly thrombogenic when exposed to the blood stream. The new purified submucosa also provides a barrier between the metallic stent and vascular smooth muscle, inhibiting late restenosis. Finally, the purified submucosa layer covers the old, diseased inner lining of the vessel (tunica intima), substituting a smooth, non-thrombogenic surface, into which healthy new endothelial cells can grow, ultimately replacing the purified submucosa with new endothelium.

Commercially available stents that are best suited for use in accordance with the present invention are metallic (typically stainless steel or tantalum) and are carried in a collapsed form over a conventional balloon angioplasty catheter. When the balloon is inflated the stent is deployed and expanded to its working, *in vivo* size. However, other types of stents, such as self-expanding stents, can also be

used in accordance with the present invention to resurface damaged or diseased body vessels.

One purified submucosa covered stent construct suitable for use in the present invention comprises a stent having one or more pieces of purified submucosal covering the exposed external surfaces of the stent. Upon implantation into a host, the purified submucosa is held between the stent and the diseased vessel wall, as depicted in FIG.1. In one preferred embodiment, the stent 10 is positioned to the desired location in the vessel through the use of a balloon-type catheter 18. In this embodiment, a single lumen angioplasty catheter 12 having an inflatable balloon 23, which is semi-rigid or rigid upon inflation, carries a vascular stent 10 covered with purified submucosa 11. This embodiment of the invention is intended for segments of vessels without significant side branches, such as the renal arteries, the common carotid arteries, or the popliteal arteries. Because of the absence of significant side branches, the lack of perforations in the purified submucosa will not pose problems for tissue perfusion.

Returning to FIG. 2, the purified submucosa overlays both the inner and outer surfaces of the stent to cover all stent surfaces with purified submucosa. Such a purified submucosa covered stent is prepared in accordance with one embodiment by first preparing a tubular purified submucosa construct, longer than the stent (preferably twice as long as the stent). A mandrel of the appropriate size is inserted into the lumen of the tube of purified submucosa and a stent is then fashioned around the purified submucosa. The leading 25 and trailing 26 edges of purified submucosa are inverted, brought back over the exterior surface of the stent 22 and sutured together 20, as shown in cross-section in FIG.2. In this embodiment, wherein both the inward and outward facing surfaces of the stent are covered with purified submucosa, a lumen 27 is formed between the outer 19 and inner 18 layers of the purified submucosa. The lumen can optionally be filled with fluidized purified submucosa, growth factors, a heparin containing composition or other components to assist the repair of the damaged or diseased vessel.

The tube of purified submucosa used to prepare the purified submucosa covered stents of the present invention can be prepared in accordance with

procedures described in U.S. Patent Application No. 08/916,490. In one embodiment, a tube of purified submucosa is removed from a submucosa tissue source. The appropriate sized lumen of the tube of purified submucosa can be prepared by inserting a glass rod/mandrel, having the appropriate diameter, into the lumen of the tube of purified submucosa and gathering up the redundant purified submucosa and suturing longitudinally 31 along the gathered material, as depicted in FIGs. 9 and 11.

Alternatively, a sheet of purified submucosa can be used to form the tube of purified submucosa. In one embodiment, the sheet of purified submucosa is rolled up around the distal end of the catheter and the opposing lateral ends are situated to form a tube that frictionally engages the catheter. Alternatively, the graft construct can be formed to define a tube of purified submucosa having a diameter approximately the same as the catheter by wrapping the purified submucosa around an appropriately sized mandrel. The formed tube of purified submucosa can then be fixed onto the distal end of a catheter. The tube of purified submucosa is held in its cylindrical shape by sutures, adhesives, compressing the matrix under dehydration conditions, heat treating the matrix, the use of cross-linking agents or any combination thereof. In one embodiment, multiple strips of purified submucosa are overlapped with one another as they are wrapped onto the mandrel to form a multi-layered tube of purified submucosa. In accordance with the present invention, the purified submucosa can be wrapped onto the mandrel in a variety of different orientations, provided that no gaps exist between the seams of overlapped purified submucosa that would expose the surface of the mandrel.

In one embodiment, a purified submucosa covered stent construct is formed by wrapping the stent with one or more strips of purified submucosal to cover both the luminal and the exterior surfaces of the stent. For example, the strips of purified submucosa can be wrapped longitudinally about the stent, starting at one end of the stent, running along the exterior surface to the second end of the stent and then running along the luminal side, from the second end back to the first end. The longitudinal wrapping is continued around the circumference of the stent forming loops of purified submucosa that cover the exposed surface of the stent. In one

preferred embodiment, the strips of purified submucosa are wrapped longitudinally so that each strip overlaps with the previously overlapped strip. The overlapped region may range up to 75%. The width of the individual strips and the amount of overlap will vary according to the size and type of stent selected. The appropriate parameters will be selected to ensure that upon deployment of the stent the stent surface will not become exposed. Accordingly, upon expansion of the circumference of the stent, the individual loops of overlapped purified submucosa will slide over one another to allow for the increased size of the stent without exposing the surface of the stent. Hence, both the inward and outward facing surfaces of the stent remain covered with purified submucosa, and both the blood and underlying vascular wall "see" only purified submucosa.

In one embodiment (FIG. 9), an improved stent 29 comprises a conventional expandable stent 10, wherein the exterior of the stent is covered with purified submucosa 11 except for at least a portion 30 of the exterior for placement in a vessel comprising a main lumen and at least one side branch, such that an uncovered portion 30 of the exterior is placed over a side branch thereby covering the original intimal surface while not covering the side branch.

In another embodiment (FIG. 10), an improved stent 32 comprises a conventional expandable stent 10 wherein purified submucosa 11 covers the exterior of the stent and extends beyond the end 34 of the stent being suspended taut across the lumen of the stent 33 to provide a smooth non-thrombogenic surface 35 to occlude flow through the vessel. The suspension 36 may be done by suturing, gluing or other fastening methods.

In one embodiment (FIG. 12), an improved stent comprises a conventional expandable stent 10 wherein purified submucosa 11 which is longitudinally pleated 38 is attached to the external surface 39 of the stent to provide expansion of the purified submucosa where the stent is expanded.

In another embodiment, an improved stent comprises a conventional expandable stent wherein purified submucosa which is circumferentially pleated is attached to the external surface of the stent to provide a longitudinal expansion in the length of the purified submucosa as the stent expands.

Applications involving the repair of vessels that have several branches (such as the left anterior descending coronary artery, that has several smaller, but metabolically significant side branches) requires modification of the basic device. In accordance with FIG. 3, a sleeve of purified submucosa 11 is placed over a stent 10, and the covered stent is placed over an angioplasty balloon. Staggered rows of longitudinal slits 40 are cut in the purified submucosa, as shown in FIG. 3. When the balloon-stent unit is expanded, the purified submucosa opens to form a mesh 41, through which blood can pass from the central lumen into side branches.

The mesh provides a matrix for in-growth of native endothelial tissue. However, high blood flow rates, through the open spaces in the mesh where vessel side branches exist, will tend to retard thrombosis, maintaining the opening in the purified submucosal mesh. Occasional obstruction of a side branch by the substance of the mesh can occur, but by optimizing mesh size, blood flow to the side branches will be preserved.

Attachment of the slit purified submucosa to the coils of the underlying stent is accomplished by the placement of sutures through adjacent slits in the purified submucosa and around individual stent coils to form gathers of purified submucosa. As the balloon stent complex is expanded *in vivo*, the meshwork opens to the pre-planned final diameter, and the gathers are drawn taut.

Alternatively, a slitted tube of purified submucosa can be used to cover both the exterior and luminal surface of the stent to repair vessels that have several branches. In this embodiment, a slitted sheet of tubular purified submucosa, twice as long as the stent, is laid down over the surface of a mandrel, and a stent is fashioned around it. Then the leading and trailing edges of slitted purified submucosa are averted, brought back over the exterior surface of the stent and sutured together to secure purified submucosa around both the blood-facing and tissue-facing surfaces of the stent. In this case, suturing the purified submucosa to the individual coils of the stent is not necessary, the single suture line is sufficient to secure the purified submucosa in place. The stent can be fixed onto the distal end of a balloon-type catheter and when the balloon stent complex is expanded *in vivo*, the meshwork opens to allow blood to pass from the central lumen into side branches.

Deployment of a purified submucosa-covered stent, corrects two resultant abnormalities of atherosclerotic occlusive disease in one simple mechanical treatment. First, angioplasty with stent placement reverses the chronic stenosis caused by atherosclerotic plaque material. Second, resurfacing with anchored purified submucosa covers the old, complication-prone, diseased surface with a smooth, fresh, biocompatible surface that is resistant to thrombosis, fragmentation, and dissection. Furthermore, purified submucosa can be dried, stored, and rehydrated without loss of mechanical strength or thromboresistance. Thus purified submucosa can be applied to angioplasty catheters, stored in conventional sterile packages, and rehydrated at the time of use by immersion in sterile saline.

Example 1

Preparation of a Purified Submucosa Covered Stent

A segment of purified submucosa, prepared as described in U.S. Patent Application No. 08/916,490, is sized to make the diameter of the implant less than or equal to the normal caliber of expected recipient blood vessel (i.e., isodiametric). A sterile glass rod having the same diameter as that of the target vessel is selected and placed into the graft lumen. This reduced diameter allows for the initial 10 to 20% dilation that occurs after exposure to the systemic circulation and eventual isodiametric size. Redundant purified submucosa is then gathered and the desired lumen diameter achieved by using either two continuous suture lines or a simple interrupted suture line with 5-0 polypropylene suture material with a swaged, taper cut needle. The material is then fixed onto the pre-made stent-and-balloon catheter and the cut longitudinal ends are tucked under the ends of the stent or otherwise secured to the stent, for example by suturing the purified submucosa to the individual coils of the stent (see FIG. 1). The preferred stent design is one that does not change length during deployment, and thus does not create longitudinal folds or wrinkles in the purified submucosa.

Example 2

In an alternative embodiment, the purified submucosa is fixed to the stent by spiral wrapping strips of purified submucosa on a stent wire, then forming the stent, as shown in FIGs. 4, 6, and 7. The stent 10 is made by starting with a straight

wire 42 which is covered with purified submucosa 11. The wire is covered with two or more strands of dry purified submucosa 43 by braiding as shown in FIG. 4. When covered in this way, the purified submucosa is wetted and allowed to dry. Therefore, the purified submucosa is really a braided sleeve that covers the wire. Alternatively, the stent wire 42 can be coated with a fluidized form of purified submucosa and allowed to dry. The wire is bent into a stent 10 as shown in FIGs. 6 and 7.

The purified submucosa can also be fixed onto the stent wire without first cutting the prepared tube of purified submucosa into strips. After preparing the purified submucosa as described in U.S. Patent No. 4,902,508, the stent wire 42 is passed through the lumen of the prepared section of purified submucosa 44 (FIG. 5). The tube of purified submucosa will then be stretched by pulling the two ends away from each other, to decrease the diameter of the prepared tube of purified submucosa, thereby forming a closely fitting covering for the stent wire, as shown in FIG. 5. The covered wired is then coiled as in FIG. 6 to form the expandable stent.

Example 3

Implantation of Purified Submucosa Covered Stents within Dogs

Five dogs (hounds, approximately 40 to 60 lbs) will undergo a laparotomy under general anesthesia (Pentothal, i.v. and Isoflurane gas maintained at 2%) with placement of a 2-4 cm, small intestinal purified submucosa coated, 11.5 Fr. biliary stent. The stents will be Cotton Leung Biliary Stents manufactured by Wilson-Cook Medical, Inc. Of Winston-Salem, NC. Sterilized small purified submucosa is prepared in accordance with Example 1 in tubular form and having a length greater than the length of the stent. The purified submucosa is positioned within the luminal space of a stent so the two ends of the purified submucosa extend past the ends of the stent. The two ends of the purified submucosa will then be averted and pulled back over the exterior portion of the stent and sutured at the midline of the stent. Thus both the exterior and luminal surface of the stent will be covered with the purified submucosa.

This purified submucosa covered stent is then deployed in the bile duct of the dogs using the following procedure which entails a laparotomy in the dog under

general anesthesia. A midline incision from umbilicus to xiphisternum will be performed with dissection to and opening of the peritoneum performed in accordance with procedures known to those skilled in the art. The common bile duct will be identified and followed to the duodenum. A duodenotomy will be performed and the major papilla identified. After dilation of the papilla, a 24 cm purified submucosa-coated 11.5 Fr. biliary stent will be placed into the common bile duct with the distal portion of the stent protruding through the papilla and draining into the duodenum. The duodenotomy and abdominal wall incisions will be closed and the animal allowed to recover from anesthesia in an intensive care cage. The dogs will be monitored by the Medical Research Lab Animal Technicians and be allowed food and water approximately 24 hours post-operatively. Post-operative analgesia (torbutrol) will be administered as required.

No drains will be placed in the animals and the post-operative recovery needs are expected to be those encountered with exploratory laparotomy alone. Animals will be observed for signs of sepsis, jaundice, bowel obstruction, etc. and euthanized at this time if necessary. Euthanasia will be by Socumb euthanasia solution, i.v., 1 ml/10 lbs. Dogs with uneventful post-operative courses will be euthanized at approximately 12 weeks; the biliary stent will be recovered at the time of post-mortem examination of the abdomen with appropriate specimens of adjacent organs submitted for pathological examination.

Claims

1. A prosthetic device comprising:

an elongated shaped expandable member having a luminal surface and an exterior surface, wherein expansion of said member increases the circumference of said member; and

a collagen-based matrix structure removed from a submucosa tissue source on at least one of said luminal and said exterior surface of said member.

2. The device of claim 1, wherein the elongated member is a vascular stent.

3. The device of claim 1, wherein the collagen-based matrix structure comprises intestinal submucosa removed from a submucosa tissue source.

4. The device of claim 3, wherein the submucosa covers both the exterior and the luminal surfaces of the stent.

5. The device of claim 4, wherein said matrix structure comprises a strip of submucosa wrapped longitudinally about the luminal and the exterior surfaces of the stent.

6. The device of claim 5, wherein the matrix structure comprises overlapped strips of submucosa.

7. The device of claim 2, wherein the means for expanding the stent comprises a releasable spring mechanism that biases the prosthetic device to a minimal circumference.

8. The device of claim 2, wherein the matrix structure comprises fluidized submucosa disposed on at least one of the surfaces of the stent.

9. The device of claim 2, wherein the matrix structure on the stent is provided with a plurality of slits that upon expansion of the elongated member provide fluid communication between the lumen of the stent and the exterior of the stent.

10. The device of claim 1, wherein said matrix structure is purified.

11. The device of claim 10, wherein said matrix structure has a contaminant level making said purified structure biocompatible.

12. The device of claim 1, wherein said matrix structure has an endotoxin level less than 12 endotoxin units per gram.

13. The device of claim 1, wherein said matrix structure has a bioburden level less than 2 colony forming units per gram.

14. An improved vascular stent the improvement comprising disposing a collagen-based matrix structure removed from a submucosa tissue source on at least one of a luminal surface and an external surface of the stent.

15. The improved vascular stent of claim 14, wherein said matrix structure is purified.

16. The improved vascular stent of claim 14, wherein a strip of said matrix structure is wrapped longitudinally about at least one of the luminal and exterior surfaces of the stent to form loops of said matrix structure and wherein each loop of said matrix structure partially overlaps an adjacent loop of said matrix structure.

17. The improved vascular stent of claim 14, wherein the layer of matrix structure is formed as a tube and wherein the tube is provided with a plurality of longitudinal slits.

18. The improved vascular stent of claim 14, wherein the longitudinal slits are approximately uniform in shape and are located equidistant from one another.

19. The improved vascular stent of claim 14, wherein the stent is covered by twisted or braided strips of said matrix structure.

20. The improved vascular stent of claim 14, wherein said matrix structure has a contaminant level making said purified structure biocompatible.

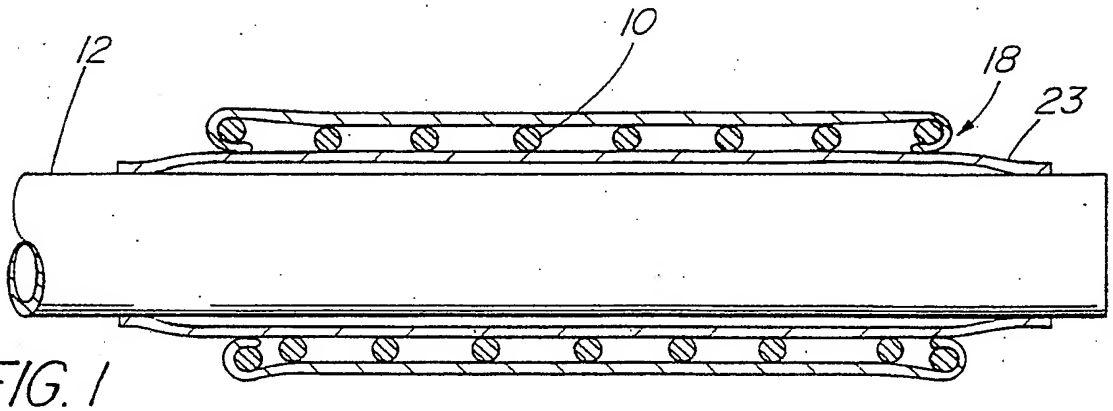

FIG. 1

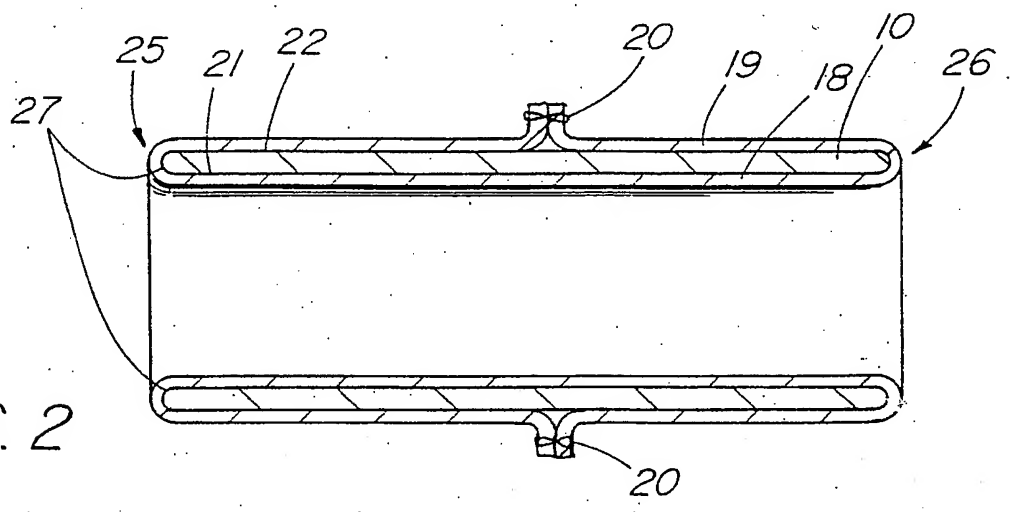

FIG. 2

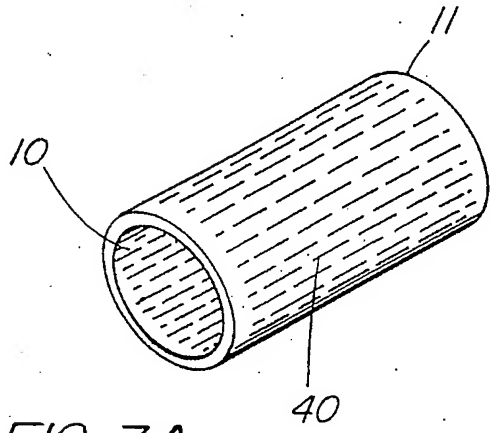

FIG. 3A

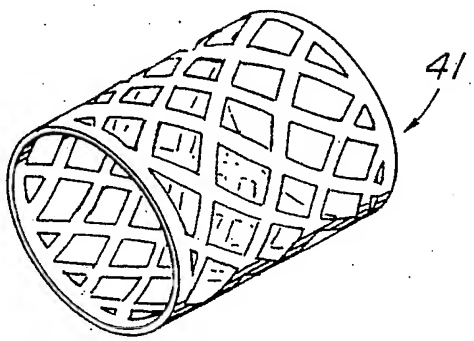

FIG. 3B

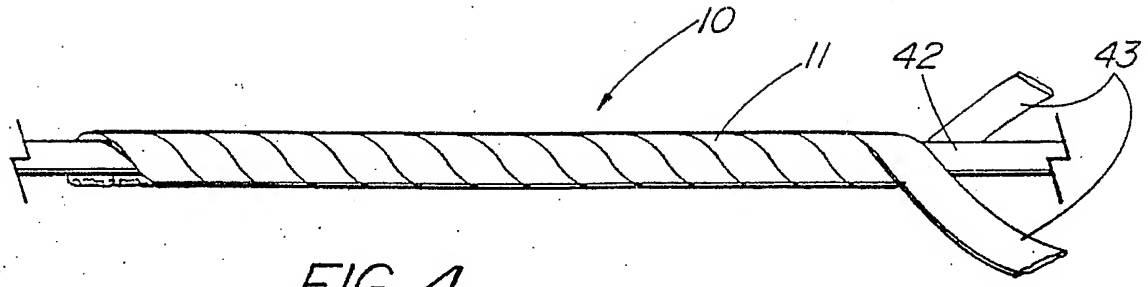

FIG. 4

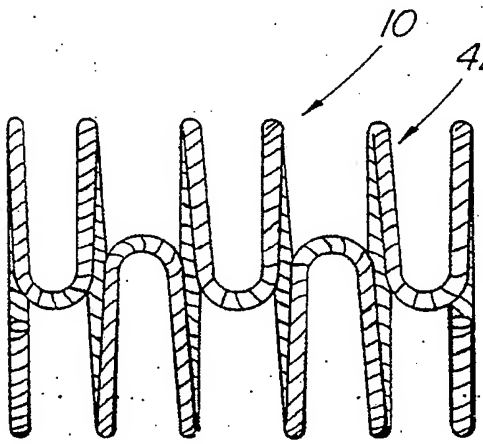

FIG. 6

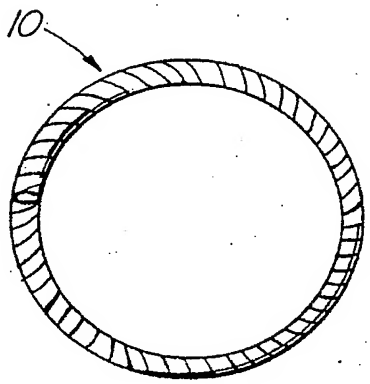

FIG. 7

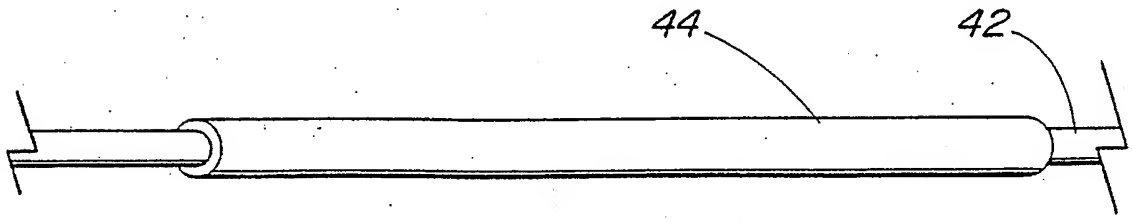

FIG. 5

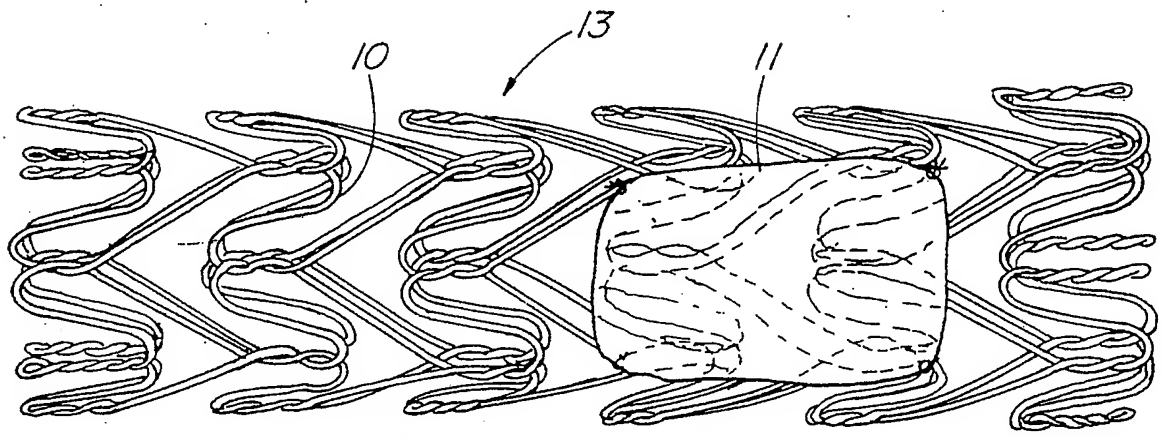

FIG. 8

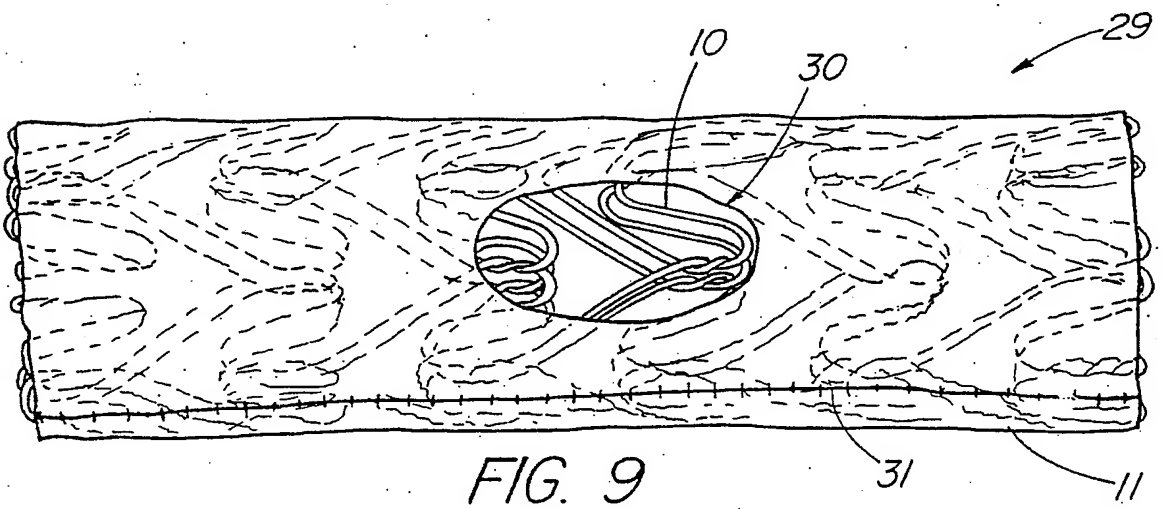

FIG. 9

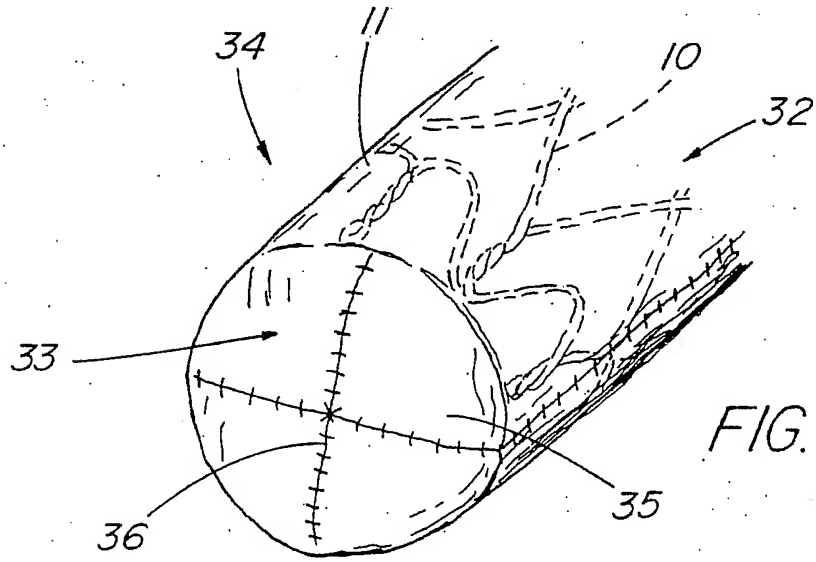

FIG. 10

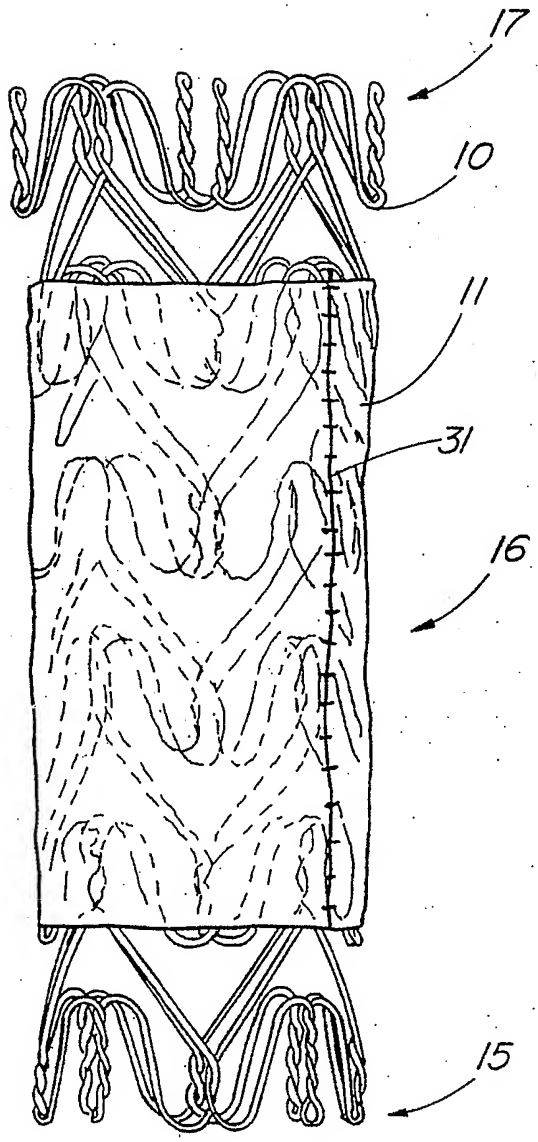

FIG. 11

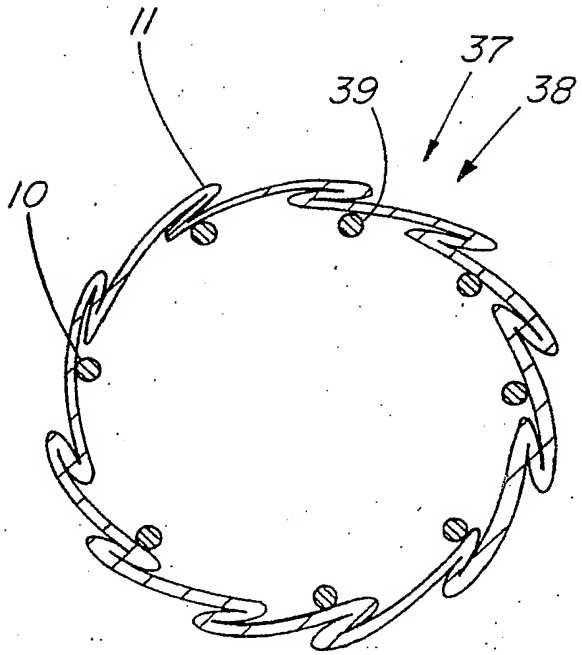

FIG. 12

INTERNATIONAL SEARCH REPORT

Inte.. .ional Application No
PCT/US 97/22751

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61F A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No..
X	8th Congress of the International Cardiovascular Society. Vienna, 6-9 September 1967 XP002062403	1-4,8, 10,11, 14,15
Y	---	7
Y	US 5 192 307 A (WALL) 9 March 1993 see the whole document	7

A	US 4 902 508 A (BADYLAK ET AL) 20 February 1990 cited in the application	

A	WO 96 31226 A (PATEL ET AL) 10 October 1996	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 1998	06/05/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Smith, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 97/22751

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